DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 2/15/2008 is acknowledged.

Claims 1-20 are pending. Claims 8-20 are withdrawn as being drawn to nonelected inventions. Claims 1-7 are currently under examination.

Information Disclosure Statement

The information disclosure statements filed on 2/14/2005, 10/11/2005, and 4/21/2006 have been considered. Initialed copies are enclosed. The Ueda *et al.* reference from *Gene and Medicine* on the information disclosure statements filed on 2/14/2005 has not been considered as no translation has been made available.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: 1A, 1B, 3A, 3B, 9A, and 9B. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 1 is objected to because of the following informalities: the claim contains the phrase "vector containing at least following five DNA sequences." The word "the" should be between "at least" and "following." Appropriate correction is required.

Claim 4 is objected to because of the following informalities: the claim recites the term "E.coli." Scientific names should be italicized or underlined and there should be a space between the period and the word "coli." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is rendered vague and indefinite by the phrase "wherein the vector is a phage vector or phagemid vector of E. coli." It is not clear whether the limitation "of E. coli" is meant to apply to the phagemid vector and to the phage vector or whether it is meant to apply only to the phagemid vector.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janda *et al.* (WO 00/71694, 2000, IDS filed 2/14/2005) in view of Lowman *et al.* (Biochem., 30:10832-10838, 1991).

The instant claims are drawn to a vector containing at least following five DNA sequences: (1) a DNA sequence encoding one protein or its fragment; (2) a DNA sequence encoding a protein for displaying said one protein or its fragment on a phage; (3) a DNA sequence encoding another protein or its fragment; (4) a stop codon that enables display switch by a host strain; and (5) a DNA sequence encoding a protein for displaying said another protein or its fragment on the phage, the vector having a structure comprising these 5 DNA sequences in the order of (1), (2), (3), (4) and (5) or (3), (4), (5), (1) and (2) in the 5'-3' direction of the vector, by the presence of the stop codon that enables display switch by said host strain, when the vector is introduced into a suppressor-mutant host strain, the vector provides a two-protein displaying phage on which both of said one protein or its fragment and said another protein or its fragment are displayed, and when the vector is introduced into a non-suppressing host strain, the vector provides a one-protein displaying phage on which only said one protein or its fragment is displayed and said another protein or its fragment is secreted into the culture medium (claim 1); wherein said one protein is a VH fragment of an antibody and said another protein is a VL fragment of an antibody (claim 2) or where said one protein is a VL fragment and said another protein is a VH fragment (claim 3); wherein the vector is a phage vector or phagemid vector of *E. coli* (claim 4); wherein the phage display protein for displaying said one protein is the pIX protein of a filamentous phage and the phage display protein for displaying said another protein is the pVII protein of a filamentous phage (claim 5) or wherein the phage display protein for displaying said one protein is the pVII protein of a filamentous phage and the phage display protein for displaying said another protein is the pIX protein of a filamentous phage (claim 6); and wherein the stop codon that enables display switching is an amber codon (claim 7).

Janda *et al.* disclose cloning vectors which encode a first fusion polypeptide, comprising an exogenous polypeptide fused to the amino terminus of an M13 filamentous phage pVII protein, and a second fusion polypeptide, comprising an exogenous polypeptide fused to the amino terminus of an M13 filamentous phage pIX protein (page 3, lines 19-35). Said exogenous polypeptides are disclosed as immunoglobulin heavy chain variable and light chain variable domains (page 12, lines 7-12). Said vector is designed for phage display of the components of a heterodimeric protein complex (page 2, lines 15-22). The M13 phage is an *E. coli* phage.

Janda *et al.* differs from the instant invention in that they do not disclose that the vector should contain a display switch.

Lowman *et al.* disclose a phage display system in which human growth hormone is attached to a phage display protein (gIII) with an amber codon between them so that in suppressor host strains the hGH is displayed on the phage and in non-suppressor host strains the protein is secreted (page 10835, column 1, paragraphs 3-4). This display switching system is useful because the protein can be selected for its binding affinity and then sequenced and expressed from the same vector without the need to create an additional construct (page 10835, column 1, paragraph 4).

Therefore, it would have been obvious to one of ordinary skill in the art, at the time of invention, to include an amber codon in one of the phage display constructs of Janda *et al.* because the antibody fragments could be selected for their binding affinity and then sequenced and expressed from the same vector without the need to create an additional construct. In addition, in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (U.S. Apr. 30, 2007), it would have been obvious to combine elements known in the art by known methods, where in the combination, each element would have performed the same function as it did separately. In this case, it was well within the skill of the ordinary artisan to introduce an amber mutation in the vector of Janda *et al.* so that one of the fusion polypeptides could be secreted or displayed on the phage, depending on whether the phage was grown in a suppressor mutant. Each of these elements would have performed the same function as they would have separately and the results of the combination would have been predictable. Furthermore, regarding claims 2-3 and 5-6, whether the VH or the VL protein is the "one protein" versus the "another protein" as well as whether the pIX phage display protein or the

pVII protein is used with either the VH or VL protein are merely matters of design choice which would not affect the function of the molecule.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janda *et al.* (WO 00/71694, 2000, IDS filed 2/14/2005) in view of Hayashi *et al.* (Gene, 160:129-130, 1995).

The instant claims are drawn to a vector containing at least following five DNA sequences: (1) a DNA sequence encoding one protein or its fragment; (2) a DNA sequence encoding a protein for displaying said one protein or its fragment on a phage; (3) a DNA sequence encoding another protein or its fragment; (4) a stop codon that enables display switch by a host strain; and (5) a DNA sequence encoding a protein for displaying said another protein or its fragment on the phage, the vector having a structure comprising these 5 DNA sequences in the order of (1), (2), (3), (4) and (5) or (3), (4), (5), (1) and (2) in the 5'-3' direction of the vector, by the presence of the stop codon that enables display switch by said host strain, when the vector is introduced into a suppressor-mutant host strain, the vector provides a two-protein displaying phage on which both of said one protein or its fragment and said another protein or its fragment are displayed, and when the vector is introduced into a non-suppressing host strain, the vector provides a one-protein displaying phage on which only said one protein or its fragment is displayed and said another protein or its fragment is secreted into the culture medium (claim 1); wherein said one protein is a VH fragment of an antibody and said another protein is a VL fragment of an antibody (claim 2) or where said one protein is a VL fragment and said another protein is a VH fragment (claim 3); wherein the vector is a phage vector or phagemid vector of *E. coli* (claim 4); wherein the phage display protein for displaying said one protein is the pIX protein of a filamentous phage and the phage display protein for displaying said another protein is the pVII protein of a filamentous phage (claim 5) or wherein the phage display protein for displaying said one protein is the pVII protein of a filamentous phage and the phage display protein for displaying said another protein is the pIX protein of a filamentous phage (claim 6); and wherein the stop codon that enables display switching is an amber codon (claim 7).

Janda *et al.* disclose cloning vectors which encode a first fusion polypeptide, comprising an exogenous polypeptide fused to the amino terminus of an M13 filamentous phage pVII protein, and a second fusion polypeptide, comprising an exogenous polypeptide fused to the

amino terminus of an M13 filamentous phage pIX protein (page 3, lines 19-35). Said exogenous polypeptides are disclosed as immunoglobulin heavy chain variable and light chain variable domains (page 12, lines 7-12). Said vector is designed for phage display of the components of a heterodimeric protein complex (page 2, lines 15-22). The M13 phage is an *E. coli* phage.

Janda *et al.* differs from the instant invention in that they do not disclose that the vector should contain a display switch.

Hayashi *et al.* disclose a phage display system in which single-chain antibodies are attached to a phage display protein (gIII) with an amber codon between them so that in suppressor host strains the antibody is displayed on the phage and in non-suppressor host strains the antibody is secreted (page 129, column 1, paragraph 1). This display switching system is useful to avoid tedious cloning procedures after a specific phage antibody has been selected (page 129, column 1, paragraph 1).

Therefore, it would have been obvious to one of ordinary skill in the art, at the time of invention, to include an amber codon in one of the phage display constructs of Janda *et al.* because the antibody fragments could be selected for their binding affinity and then sequenced and expressed from the same vector, thus avoiding tedious cloning procedures. In addition, in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (U.S. Apr. 30, 2007), it would have been obvious to combine elements known in the art by known methods, where in the combination, each element would have performed the same function as it did separately. In this case, it was well within the skill of the ordinary artisan to introduce an amber mutation in the vector of Janda *et al.* so that one of the fusion polypeptides could be secreted or displayed on the phage, depending on whether the phage was grown in a suppressor mutant. Each of these elements would have performed the same function as they would have separately and the results of the combination would have been predictable. Furthermore, regarding claims 2-3 and 5-6, whether the VH or the VL protein is the "one protein" versus the "another protein" as well as whether the pIX phage display protein or the pVII protein is used with either the VH or VL protein are merely matters of design choice which would not affect the function of the molecule.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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